REMARKS

Applicants submit this amendment in response to the Office Action dated July 14, 2003. Claims 1-37 are pending, and claims 10-13 and 15-37 are withdrawn as being drawn to a non-elected invention. Claims 1-9 and 14 are under consideration. Claims 1 and 14 are amended herein to recite conservative amino acid substitution language as supported by the specification at page 11, lines 13-17, and no new matter is added.

Claim 3 is rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing new matter. Applicants request reconsideration of this rejection on the following grounds.

Claim 3 recites an isolated nucleic acid molecule comprising a polynucleotide encoding a polypeptide having an amino acid sequence from 1-155 or from 2-115 of SEQ ID NO:4, wherein the polypeptide has at least one conservative amino acid substitution, at least 90% identity with SEQ ID NO:4, and mitogenic activity as determined by *Xenopus* oocyte maturation assay. The Examiner states that the specification and claims as originally filed do not provide clear support for the isolated nucleic acid molecule with these properties. It is clear from the specification that the invention includes nucleic acid sequences that are modified to encode EGFH2 polypeptides having on or more amino acid substitutions. This is found beginning at page 15, line 1, continuing through page 15 and to page 16, lines 9-13, which specifically indicates that the mitogenic properties of a polypeptide having such amino acid changes can be measured using the *Xenopus* oocyte maturation assay, and page 18, lines 15 to page 19, line 1, which supports the 90% identity language for SEQ ID NO:4. The disclosure of the nucleic acid compositions at, for example, page 2, lines 19-26, is encompassed within the overall scope of the nucleic acids of the invention, despite the fact that the embodiments are described at different pages of the specification. For these reasons, reconsideration and withdrawal of this ground of rejection are respectfully requested.

Claims 1-9 and 14 are rejected under 35 U.S.C. § 112, first paragraph, as the specification allegedly lacks enablement for the full scope of the claims. The Examiner summarizes the basis of the rejection as the failure of the specification to provide sufficient guidance as to the "core structure" of SEQ ID NO:4 that is essential to maintain the mitogenic activity, and which changes can be made while retaining the same function. Applicants submit

that this is not a relevant analysis of the enablement issue, and respectfully traverse the rejection and request reconsideration thereof.

In support of this position, the Examiner cites publications that are over 12 years old, and which date back to a much earlier stage in the development of protein chemistry. (Lazar et al. Mol. Cell. Biol. 8:1247-1252, 1988, and Burgess et al., J. Cell Biol. 111:2129-2138, 1990.) These publications also are not on point, because they focus on mutations that did have an effect on function of the respective proteins (although the protein function was not, in the case of HBGF, completely lost). The issue here is not whether one of skill in the art can predict whether a selected variant protein of EGFH2 will or will not have the biological activity within the scope of the claim. The issue is whether undue experimentation is required to test such a variant for the activity that will bring it within the scope of the claims. These two issues are different.

To support the ground of rejection, the Examiner cites *In re Fisher*, 166 USPQ 18 (CCPA 1970) for the proposition that "the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute." (Office Action at page 6, lines 11-13.) In *Fisher* this statement was made in the context of the claim that recited a potency of "at least 1" International Unit of protein. The Court stated that this was an "open-ended" recitation, and distinguished it from cases involving "predictable factors." In cases involving predictable factors, according to the Court, a single embodiment provides broad enablement because other embodiments could be made without difficulty and their performance characterized by known scientific laws.

In re Fisher was decided in 1970. In the 33 years since then, the art of protein synthesis, mutagenesis, and function determination have advanced significantly, and applicants submit that by the time the present application was filed, let alone today, mutagenesis and protein expression involved routine predictable factors, governed by "known scientific laws," such as the amino acid resulting from a mutagenic event at the DNA level. Only the outcome is unpredictable, and that is where experimentation enters the picture. Furthermore, such experimentation is permitted, as long as it is not undue, and the factors for determining undue experimentations are clearly described in *In re Wands*, 8 USPQ 2d 1400 (CAFC 1988). If the present Examiner's reasoning were applied to the technology at issue in *Wands*, it would require one of skill in the art to design a monoclonal antibody from the amino acid sequence all the way

up to the 3D structure, and to identify a core structure that would allow binding affinity within the claim scope. That is not the reasoning in *Wands*. Instead, *Wands* provides for the production of numerous antibody molecules of unknown amino acid sequence, but which nevertheless shared the testable functional characteristic of binding Hepatitis B surface antigen with the claimed high affinity constant.

The main issue in *Wands* was whether it was undue experimentation for one of skill to make hybridomas and screen them to determine which ones secreted antibodies within the scope of the claims. There was no expectation that all hybridomas would secrete appropriate antibodies; on the contrary, the Court clearly stated, "[p]ractitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody." (8 USPQ 2d at 1406, emphasis added.) Furthermore, an entire "experiment," according to the Court, entailed "immunizing animals, fusing lymphocytes from the immunized animals with myeloma cells to make hybridomas, cloning the hybridomas, and screening the antibodies produced by the hybridomas for the desired characteristics." (8 USPQ 2d at 1407.)

By analogy, the present invention entails making conservative substitutions in an amino acid sequence of a protein, the full amino acid sequence of which is provided by the inventors. As indicated in the documents cited by the Examiner, specifically Burgess et al. and Lazar et al., mutation of amino acids in proteins has been known for many years. The only actual screening called for in the present case is the *Xenopus* oocyte maturation assay. The details of such assays are already of record in this application. The Examiner has agreed that the issue is not how to determine biological activity of EGFH2. (Office Action, page 4, third full paragraph.) However, neither *Wands* nor *Fisher* supports the Examiner's assertion that prediction of what changes can be tolerated with respect to the functional aspects of EGFH2 is the issue. (Office Action, page 5, lines 3-7.) Instead, both decisions focus on the experimentation that might be required to determine if the candidate (in *Wands*, a hybridoma secreting antibody in the present case, a human EGFH2 polypeptide with one or more conservative amino acid substitutions) retains the function that brings it within the scope of the claims. Prediction of the structure prior to performing the experimentation does not play a role, so the Examiner's assertions at page 5, main paragraph, are not on point. As the same experimentation would be performed regardless of the actual amino acid substitution(s), the

alleged limited number of working examples also is not on point. The relevant working example is measurement of *Xenopus* oocyte maturation, and the sufficiency of this assay has not been challenged by the Examiner.

For the foregoing reasons, reconsideration and withdrawal of the rejection are respectfully requested.

All of the claims remaining in the application are now clearly allowable. Favorable consideration and a Notice of Allowance are earnestly solicited.

If questions remain regarding this application, the Examiner is invited to contact the undersigned at (206) 628-7650.

Respectfully submitted,
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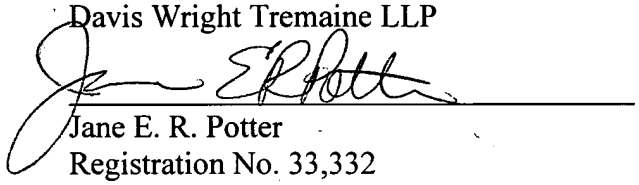

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